MEDICINE

Epinephrin From the Suprarenal Capsule

"A Classic of Science"

Dr. J. J. Abel, President of the American Association For the Advancement of Science, Isolated Epinephrin

ON EPINEPHRIN, the Active Constituent of the Suprarenal Capsule and its Compounds. By John J. Abel. In Proceedings of the American Physiological Society, Eleventh Annual Meeting, New York, Dec. 28, 29, *and* 30, 1898.

ACTING on Hyrtl's suggestion that *epinephris* would be the best name for the suprarenal capsule, the author has given the name Epinephrin to the active principle as isolated by him. . . .

The Active Principle

ON THE BLOOD-PRESSURE-RAISING CONSTITUENT OF THE SUPRARENAL CAPSULE. By John J. Abel, M. D., and Albert C. Crawford, M. D. In Johns Hopkins Hospital Bulletin, No. 76, *Vol. VIII, Baltimore,* 1897.

Both clinical experience and laboratory research have shown that the suprarenal capsule is an organ of vital importance.

Physiologists have proved that a very small quantity of an aqueous extract of the medullary substance raises the blood pressure to a great height above the normal. It has also unequalled power in reviving a poisoned heart. Gottlieb, for example, has shown that it will revive the heart of a rabbit which has practically stopped beating in consequence of an intravenous injection of chloral hydrate.

Bates applied an aqueous solution to the eye and found that it exerted a marked vaso-constricting action. In numerous cases of congestion a small quantity dropped into the conjunctival sac brought about an immediate pallor, lasting for some time. According to this writer the extract is very useful in prolonged operations, for, when repeatedly applied, hemorrhage is prevented and cocaine anaesthesia is in consequence indefinitely prolonged. As the result of his two years' use of the extract Bates concludes "that within the limits of its sphere of activity there is absolutely no other substance which can take its place."

Other experiments go to show that the aqueous extract is a powerful poison when injected directly into the circulation and may lead to fatal results.

The various extracts that have been used in these experiments were mixtures of unknown substances, and it is as yet an unsolved question whether the various actions at present ascribed to the gland are due to one and the same substance.

We are at present interested in the isolation of the blood-pressure-raising constituent, for in a purified state, separated from all other constituents, it might become a therapeutic agent of great importance.

On the chemical side but little advance has been made over Vulpian's striking original contribution more than forty years ago. Vulpian observed that the juice expressed from the suprarenal capsule of many different animals behaved in a striking manner toward ferric chloride and toward solutions of iodine, giving with the former reagent an emerald green color, and with the latter a beautiful carmine tint. No other tissue of the body, so far as investigated by Vulpian, gave these reactions. . . .

[A list of tests for various chemical groups made upon the extract by many investigators follows.]

There is therefore at present great diversity of opinion as to the chemical character of the blood-pressure-raising constituents of the gland.

Whatever the probability may be of the correctness of this or that view, it is to be noted that all of the above-named investigators have based their conclusions on reactions made with aqueous, alcoholic or acetonic extracts; none of them have even roughly isolated a definite chemical compound. The subject is one of great difficulty, and our own work is at present merely preliminary, but we have arrived at the following conclusions which we believe to be borne out by our experiments.

First, we have found by isolating the blood-pressure-raising constituent in the form of a benzoyl compound and decomposing it, that the active principle is a substance with basic characteristics and that it must in all probability be classed with the pyrrol compounds or with the pyridine bases or alkaloids.

Second, that pyrocatechin cannot be split off from the isolated active compound by boiling with acids, as has been asserted.

Third, we have found that a carmine-red pigment can be separated from the sulphate of the active principle without destroying its power to raise the blood pressure.

Fourth, in addition to this, we have isolated from the crude benzoyl product a volatile basic body which fumes in the air and which emits an odor very much like that of coniine. . .

Blood-Pressure-Raising Constituent

We have now obtained the active principle in the form of a sulphate. As thus far isolated it is a hygroscopic, straw-colored residue which tends to crystallize on standing over sulphuric acid, agglomerates of small crystals forming on the edge of the bowl and the entire residue taking on a semi-crystalline appearance. This sulphate does not contain the volatile coniine-like substance, nor do we find the carmine-red pigment which falls out on the addition of an alkali. Alkalies no longer liberate the coniine-like substance nor do they throw out the red pigment, but they cause a brownish discoloration, and on heating, alkaline vapors, probably ammonia, are given off. . .

Although somewhat contaminated with its own decomposition products, this final sulphate has all the characteristics of an active substance. As shown by repeated experiments, it promptly raises the blood pressure, it constricts the vessels of an inflamed eye, and when injected into the dorsal lymph sac of the frog it acts like a narcotic or cerebro-spinal poison.

As freed of the red substance the sulphate of the active principle behaves as follows: It is very soluble in water, fairly soluble in weak alcohol (50 per cent.), almost insoluble in absolute alcohol, and quite insoluble in ether, acetone, ligroine and chloroform. Its aqueous solution, even when freed from adherent sulphuric acid, has a slightly acid reaction. The addition of iodine water to a neutral solution does not give a rose-red color. Alkalies added to a strong solution give a brown color which deepens on heating. Ferric chloride gives a purplish brown, almost black in concentrated solution, which on the addition of tartaric acid and an alkali passes into a deep red color. Before the removal of the carmine-red substance the addition of ferric chloride gives the well-known emerald green color, which passes into red on the addition of an alkali.

It is evident that our sulphate gives Vulpian's ferric chloride reaction, though somewhat changed by the removal of what we take to be the chromogenic substance which gave his iodine reaction. It also promptly reduces silver nitrate in alkaline solution, but does not reduce Fehling's solution even on boiling.

Relation to Alkaloids

More than a year ago, during our first studies with suprarenal extract, we were struck with the fact that every extract entirely free of proteids and physiologically active gave a fine pyrrol reaction when subjected to dry distillation. This is evidenced both by the odor and by the pine sliver reaction. A small quantity of the isolated sulphate also gives the pyrrol reaction when heated either alone or with zinc dust.

We attach considerable importance to this reaction. As is well known, alkaloids in general give pyrrol on dry distillation; morphine, for instance, on being heated with 10 parts of zinc dust gives off pyrrol, ammonia, trimethylamine, pyridine, phenanthrene, etc.[1] During the past winter we made several attempts to prove the presence of pyridine among the products of dry distillation of the active principle as above isolated, as its detection would prove that our principle was to be classed among the alkaloids. . .

Summary

We may summarize the results of our work as follows:

The blood-pressure-raising constituent of the suprarenal capsule may be completely precipitated from an aqueous extract by treatment with benzoyl chloride and sodium hydrate, according to the Schotten-Baumann method.

On decomposing the resulting benzoyl products, a residue is obtained which possesses great physiological activity. It gives the color reactions of Vulpian, reduces silver nitrate and possesses the other specific qualities of suprarenal extracts.

With the help of alkalies a carmine-red pigment may also be separated from these decomposition products. We take this pigment to be that one of the chromogenic substances of Vulpian which gives the rose-carmine color when suprarenal extracts are treated with oxidizing agents or alkalies.

A volatile, basic substance of a conine-like odor is always found to accompany the crude benzoate. When these substances are removed the active principle is left as a highly active sulphate or hydrochlorate, as the case may be. It is therefore a basic substance. Its salts give a color reaction with ferric chloride; they also reduce silver nitrate, but not Fehling's solution.

It is not possible to split off pyrocatechin from this isolated active principle. The fact that dry distillation causes the appearance of amines and pyrrol in abundance, taken in connection with its ability to take up acid radicles, its reducing power, its precipitability by cupric acetate and iodine chloride, and its physiological action, lead us to conclude that our active principle is to be classed with the pyridine bases or alkaloids.

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[1]We are well aware that certain salts of glutaminic, pyromucic and its related acids also yield pyrrol on dry distillation. These compounds, however, like the proteids and their allies, appear to us to be excluded.

ENTOMOLOGY

Insects Artificially Digested To Determine Skeletal Weight

HOW MUCH does an insect's skeleton weigh?

This question has been accurately answered for the first time by Patrick Alfred Buxton, of the London School of Hygiene and Tropical Medicine.

Like many other scientists who make it their business to find out all they can about the lives of insects, he wanted to know as much as possible about their vital functions. He has been experimenting by exposing them to different conditions of dry and moist atmospheres, determining what sort of exposure does them the most harm. Yet many times, after he had noticed that insects lost both water and dry-material weight after exposure, he found himself faced with the problem:

Insects First Dried

"How much of what remains of this insect is living matter on which it could perhaps call for energy, and how much of it is 'dead' skeleton?"

He determined to find out.

Insects do not have large, bony skeletons like higher animals. Much of their "skeletons" are made of chitin, the horn-like substance that forms their shells and stings and sheaths. Mr. Buxton could not simply dissect an insect, take out all its bones, and weigh them.

Selecting a bunch of fat meal-worms, he dried them out and removed all the fat with ether. The rest he put first into pepsin and then into pancreatin, which are two digestive juices. He had to powder the little dried bodies and break up the legs, and then coat them with a liquid that would make them sink in the juices. And so he let them digest—literally, just as they would be digested in the stomach of an animal—for three or four days. What was left, he weighed.

New Method for Suckers

When he came to use blood-sucking insects, however, he found that his digestive juices would not dissolve haematin, the dried blood-substance. He had to work out another method. Back he went to his meal-worms and using the results obtained by digesting for comparison, he found that dissolving powdered dried insects in potassium hydroxide solution at the boiling point for 24 hours would give the same results. And potassium hydroxide will dissolve haematin.

About one-twelfth of the body of a meal-worm is skeleton, Mr. Buxton discovered, but that is not the important thing. Other scientists now have, thanks to his work, a method by which they can find the skeletal proportion of any insect—if they ever happen to want to.

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